Imaging of pain: recent developments

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Brain imaging of pain has made remarkable strides in the past year and a half. The basic regional activation pattern after acute nociceptive stimulation is now fairly well clarified. The extension of imaging studies from normal subjects to include cohorts of pathological pain patients is occurring. The techniques of positron emission tomography, functional magnetic resonance imaging and single photon emission computed tomography have all been applied to the study of human pain processing and the assessment of physiological interventions or psychological manipulations. Studies using labelled ligands to trace receptor alterations have also been conducted. Although more work could be done on the pharmacology and physiology of anesthesiology, the resulting set of observations provides a deeper understanding of the basic human neurophysiology of pain and a potential neural framework for better pain management. Curr Opin Anaesthesiol 12:583–589.

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Abbreviations

ACC	anterior cingulate cortex
fMRI	functional magnetic resonance imaging
PAG	periaqueductal gray
PET	positron emission tomography
SI	primary somatosensory cortex
SII	secondary somatosensory cortex
SPECT	single photon emission computed tomography

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Introduction

The neural activity that can be imaged in the human brain by nociceptive stimulation represents a multiplicity of functions [1••]. Among these are sensory and motor integratory functions to perceive the stimulus and formulate an appropriate response. In addition to the two main functions of perception and escape, which are of prime adaptive significance, a variety of other neural subroutines are engaged that play roles related to the stimulus characteristics (e.g. warm versus hot), the context and other hierarchical processes [2].

Imaging has also identified regional activations in anticipation of a painful stimulus [3•,4•], influences of other variables such as gender [5•], and modulation by psychological manipulations such as hypnosis [6••]. Technical advances in functional imaging are now permitting more elaborate and clinically relevant studies. For example, the introduction of more sensitive positron emission tomography (PET) using scanners without collimating septa has enabled more scans to be performed. This makes single subject studies with PET a reality and allows unique clinical cases to be examined in a reliable fashion. Furthermore, the whole field of functional magnetic resonance imaging (fMRI) is rapidly expanding. In this review we will examine issues in general terms and provide interpretation. A total of 55 papers were identified, most are somatosensory studies with experimental nociceptive stimulation applied to the body surface, and this review largely concerns these papers (n=25: 13 PET, 12 fMRI). Ten papers covered various aspects of headache and migraine (seven PET, three fMRI). The assessment of brain function using blood flow tracers of one type or another formed the majority of the reports (n=50). Comparatively few studies (n=5) measured neurochemical parameters such as receptors; all of these were concerned with opiate receptors in the brain. Six studies examined neural activation in pathological pain states (four PET, two fMRI). What is evident from these numbers is the strong exploration of fMRI as a technique to study pain. All of the functional activation studies utilize the coupling between increased neural activity and increases in local blood flow as the basis of the measurement for pain-induced activity.

This review focuses on studies in which pain is the central subject of investigation. Imaging studies of headache are not considered because they mainly investigate mechanisms of vascular [7–9] or brain structural abnormalities [10] rather than pain *per se*.

Comparisons of foci of activation between studies have been compiled and discussed in several studies [1••,5•,11,12••]. We will, therefore, try to limit our own tendency to elaborate compilations of neuroanatomical information. We apologize in advance for any degree of perceived idiosyncratic views. A perusal of the discussion sections from the referenced papers, however, will reveal many shades of interpretation for particular results.

Pain regional activations: positron emission tomography studies

PET studies of pain have examined a variety of stimuli and stimulus characteristics: hot and cold painful thermal stimuli, phasic and tonic application, delivery by contact thermode, carbon dioxide laser, or chemical or visceral stimulation. From compilations of these data a 'map of pain' has emerged. This map is composed of several characteristic regions; some are obviously related to the sensory aspects, as expected from classical anatomical and physiological studies of pain. Other regions have a less clear relationship to pain and their role needs to be defined. As the number of regions detected and the number of manipulations per study increased, attempts have been made to organize this information into a comprehensible set of systems [1••,2]. The objective of this categorization is to provide a framework for discussion and orientation, and interpretation should be neither overly simplistic nor overly rigid. For example, some areas such as the anterior cingulate cortex and thalamus, with their multiplicity of connections and individual sub-regions or nuclei, are obviously involved in more than one function.

The basic pain network is composed of approximately four functional groupings [1••]. The first is a sensory–perceptual component that includes the primary and secondary somatosensory cortices (SI and SII), portions of the thalamus and portions of the insular cortex. The role of the SI is discussed by Bushnell *et al.* [12••] and Treede *et al.* [13•]. One notable finding from our chemically induced pain studies (i.e. no tactile component) is that direct activation of peripheral C-fibers with capsaicin primarily activates the SI, with little activity observed in the SII, whereas tactile or vibratory stimulation activates the SII preferentially over the SI [1••]. Studies in which a contact thermode is used convolve the touch and pain components to such an extent that it is difficult to subtract out the touch component from the combined presentation. Thalamocortical and cortico-cortical functional connectivity thus needs to be re-assessed with the differential touch versus pain activation in mind. The debate as to whether the SI is activated or not with a pain stimulus should be laid to rest [12••,14•]. Studies that do not obtain SI activation probably did not contain a large enough number of subjects or had other technical limitations. For some stimuli, blood flow may not be the relevant parameter to measure. In addition, spatial and functional factors may be involved because differences in the spatial arrangement of the postcentral gyrus and the somatosensory homunculus can impose a functional–spatial separation that may make stereotaxic normalization more difficult than usual. It is also worth noting that a pain homunculus exists in the SI, as can be gleaned from the foci of activation from several studies [1••,2,14•,15,16].

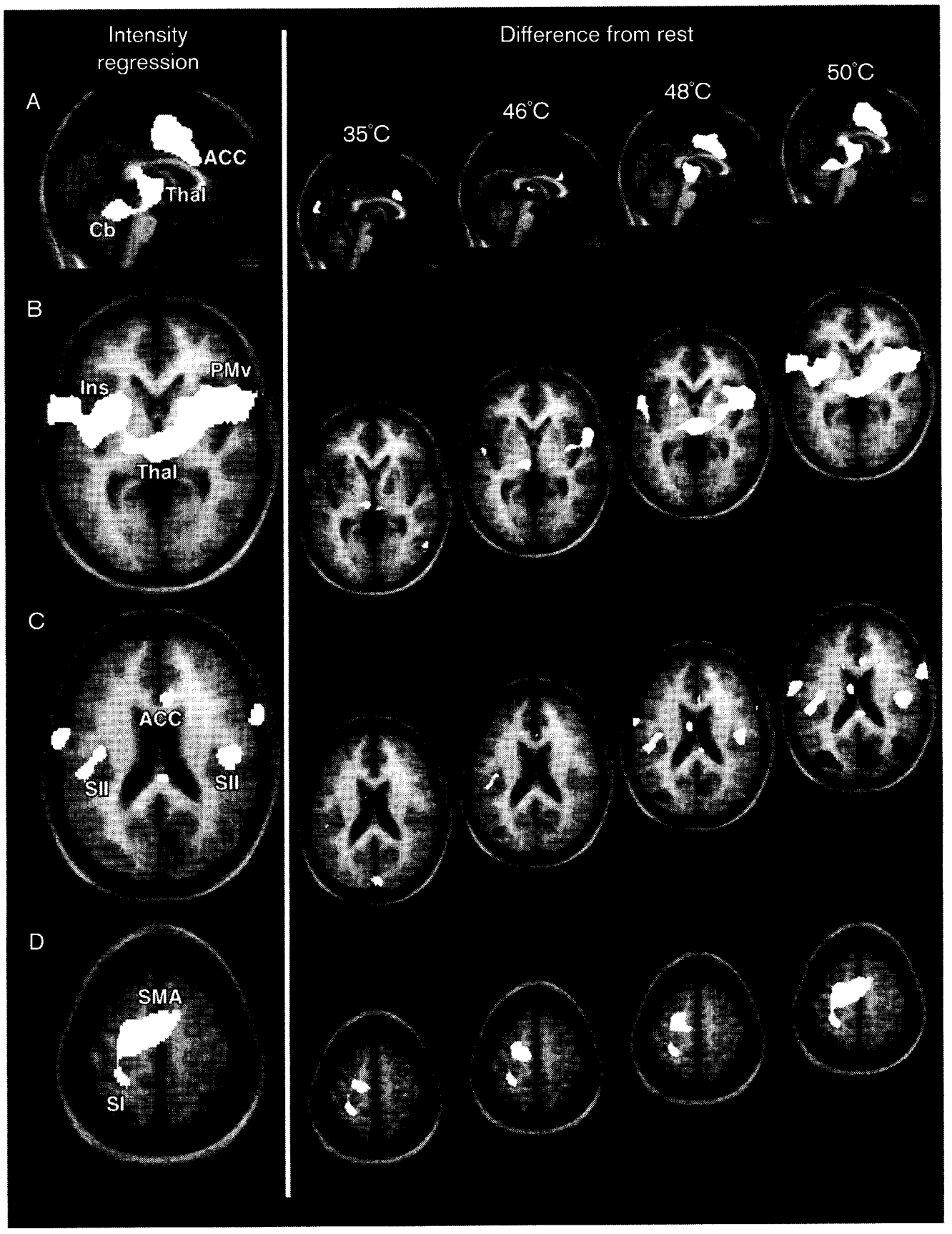
The thalamus and insula deserve further comment. Many studies using strong pain stimuli [2,14•,15] see bilateral activation of the thalamus with foci in multiple thalamic nuclei, notably the dorsal medial nucleus. The neurons within these activated nuclei send projections to a multiplicity of cortical regions, many of which also show activation (e.g. insula, posterior parietal, anterior cingulate, SI, SII). A great degree of interconnectivity can thus be postulated. In contrast to pain, light touch and vibration produce a barely detectable signal in the thalamus [1••]. The low level of activity suggests that the thalamus performs a simple relay function for these somatosensory stimuli, with little synaptic load being placed on the region. In contrast, pain places a much more marked synaptic activity, energy demand and blood flow change. The biochemical mechanisms underlying increases in neural activity and energy demand were recently discussed [17••,18•].

The insular cortex is a very large region of brain tissue with multiple subdomains that are cytoarchitectonically distinct with distinct functions [see Refs 1••,5•,14• for discussion and references]. Therefore, treating it as a single entity or placing 'the insula' in any one category is premature. Some of the distinct functionality is beginning to be teased out by studies in which various cognitive or psychological factors are investigated. For example, a recent fMRI study [4•] demonstrated two domains activated in the anterior insula, one during pain stimulation and a spatially distinct region active during the anticipation of pain.

The second component of the basic pain network is a motor integratory group that includes the supplementary motor cortex, putamen, globus pallidus, several regions in the cerebellum, the cerebellar deep nuclei, and mesencephalic regions consistent with the red nucleus and superior colliculus. Figure 1 shows the progressive recruitment of many of these regions (e.g. the putamen–globus pallidus) as pain intensity increases [19]. All of the motor regions are consistent with the concept of motor planning and incipient or intended postural orientation to the applied stimulus.

A third system is an attentional component composed of the anterior cingulate cortex (ACC) and other brain

Figure 1. Stimulus-response characterization of pain activations



Stimuli were delivered via contact thermode to the upper right arm. Activations are in white and are superimposed on the average structural MRI of the subjects. The right set of sections shows subtraction images comparing resting state non-stimulated condition to neutral temperature (35°C) and successively more painful thermal stimuli of 46°C (mild pain), 48°C (moderate pain) and 50°C (intense pain). The panel shows pain-intensity dependent activations determined with a regression analysis. Note the similarity of the pain intensity map to that obtained with 50°C. These data show the progressive recruitment of the pain network as pain intensity increases. Furthermore these data provide strong evidence for a parallel distributed mechanism of cerebral pain processing [19].

regions. However, as with the insula, classifying the ACC as solely mediating attention is to understate the multifactorial role of this very large cortical region. Two to three distinct areas in the ACC are activated, Brodmann area 24 very consistently between studies and a more anterior perigenual area (see Fig. 1). The ACC is also implicated in mediating the affective component of pain as well as being involved in motor integration. Several studies have tried to tease apart the multiple potential roles of the cingulate. Comparison pain to another cognitive task, the Stroop test, was used to characterize the spatial coordinates of pain activation and cognitive activation (the ACC is activated by many cognitive tasks) [20•]. Different, but adjacent, ACC regions appeared to be activated in the two conditions. However, the study design did not rule out the possibility that one locus subserved the attention component of pain and the other locus the attention component of the cognitive task. A study by Rainville *et al.* [6••] and a previous one by the same group [21] used hypnotic suggestion to bias the subject's perception of pain unpleasantness (affective component). The 1997 paper [21] presented data indicating that a hypnotic suggestion to increase unpleasantness in response to a pain stimulus increased ACC activity above the non-biased control. However, the design did not rule out the possibility that the differential activity could be caused by directed attention. A comparison with a hypnotic

suggestion to increase pain intensity may have clarified the selective role of affect versus attention in the study. The 1999 paper [6••] is more of a treatment of neural mechanisms of hypnosis, and documents several extremely interesting processes related to hypnotic induction and increases in regional cerebral blood flow in the occipital cortex.

A fourth system is related to descending control. Several groups have reported activation of the mesencephalic periaqueductal gray (PAG), consistent with the idea that descending control processes can be activated during the administration of experimental pain stimuli [1••,3•]. One study of anticipatory coping mechanisms [3•] demonstrated activation of PAG during the anticipation of an unpredictable and unlearned pain stimulus, but not during the anticipation of an inevitable, predictable (learned) pain stimulus.

It is important to ask what other organizational principles can be derived from these data. Several other regions are activated in various studies, such as the left or right prefrontal cortex and the posterior parietal cortex. The contribution these regions make to pain processing becomes harder to specify the higher up the neuraxis they are. In order to examine some of the higher order organizational aspects, such as the apparent parallel and distributed arrangement, we examined a stimulus–response paradigm [2]. That parametric study examined 16 subjects who underwent five scan conditions: resting state, 35°C (neutral), 46°C (mild pain), 48°C (moderate pain) and 50°C (substantial pain), each repeated twice. The PET data were subjected to several multiple regression analyses to identify pain intensity-dependent and pain intensity-independent regional activations. The pain intensity-dependent activations constitute the basic pain map described above. The graded activation of the network as a whole suggests that pain intensity information is recognized in a distributed network of interconnected areas. We also detected two regions in the prefrontal cortex that showed a pain intensity-independent activation. These areas are coincident with the dorsolateral prefrontal sites involved in working memory, and activations here were partly hypothesized to mediate the cognitive/evaluative aspects of the paradigm. Therefore, activity in some regions is driven by pain intensity whereas activity in other regions reflects the non-sensory aspects of the stimulus [see also Ref. 14•].

Additional studies have examined tonic activation with noxious heat [22], and differences in pain regional activation between the sexes [5•,15]. Pain-induced blood flow changes, as measured with single photon emission computed tomography (SPECT), has been used to probe the pain state resulting from spinal cord injury [23•], phantom limb pain [24] and pain resulting from familial restless legs syndrome [25]. Clear evidence of thalamic activation was seen in all of the studies. The use of SPECT was reviewed by Mountz *et al.* [26]. Two studies on pain-induced blood flow changes have been performed in animals. The SPECT tracer [^{99m}Tc]exametazime also has been used for autoradiography in rats during acute and tonic phases of the formalin test [27], and PET imaging has been performed in anesthetized cats during joint activation with and without inflammation [28].

Figure 1 summarizes the 'pain map' in two ways: on the left are the regional activations as revealed by the regression against perceived pain intensity. Significant activations are shown in white, deactivations (mainly in the occipital poles) are not emphasized and are rendered in grayscale. On the right are a series of subtraction analyses compared with the resting state, showing the progressive activation within the network as perceived pain intensity increases and the thermode temperature increases. Although all of these regions are not necessarily involved in discriminative processing, the fact is that the intensity information drives activity within the network on both the input (sensory) and output (motoric) sides.

Central pain and mechanisms of pain control, in addition to hypnosis, have also been examined using functional PET imaging [29–31]. The sensation of allodynia, as a result of lateral medullary infarct, was accompanied by clear activation of the thalamus, SI and SII, and inferior parietal lobule [29]. However, the same tactile cold rubbing of the skin on the normal side was perceived as non-painful and produced little activation of the somatosensory network. One conclusion is that somatosensory neural systems have undergone plastic modification, such that allodynia produces an exaggerated increase in activity in comparison to the normal response to the 'innocuous' stimulus. A human model for allodynia has been examined using PET [1••], and comparisons of allodynia to resting state versus light brush to resting state also show exaggerated blood flow responses. These studies highlight the need carefully to dissect out regional activations caused solely by touch and versus pain. The motor cortex and thalamus have been stimulated in efforts to relieve chronic neuropathic pain [30,31]. PET imaging performed during the stimulation has shown activation in several areas synaptically connected with the stimulation site (e.g. the motor cortex activated the thalamic ventral anterior and ventral lateral nuclei and thalamic stimulation activated the insular cortex). Although the significance of the results in terms of pain relief may not be readily apparent, those studies represent real progress in examining the neural mechanisms of stimulation-based pain relief in a difficult patient population.

Pain regional activations: functional magnetic resonance imaging studies

Magnetic resonance imaging is an extremely versatile set of techniques for brain imaging. The most familiar use is structural brain imaging for the identification of lesions. However, over the past 10 years functional brain imaging using blood flow methods (fMRI) and the imaging of certain biochemical moieties has been implemented. Several studies using blood flow or blood volume measurements have been applied to the study of pain systems in the central nervous system. Most of the groups using fMRI are working through what could be called the 'basics of pain', and the studies to date tend to recapitulate what has been done previously using PET. The stimuli included hot and cold thermal, cutaneous electrical, esophageal distention, and chemical stimulation by subcutaneous injection of an acidic solution [32••,33,34••,35•,36,37]. Neural mechanisms of pain relief stratagems using deep brain stimulation with thalamic electrodes and dorsal column stimulation have also been investigated [38,39]. In general, those studies have corroborated the regional activation network delineated using PET and discussed above. It is worthwhile to ask what this technique has added or will add to the field. First, it must be recognized that fMRI is not one technique. It is a variety of evolving methodologies that can be applied with various levels of spatial and temporal resolution. A variety of questions can thus be posed and investigated, often using a set of sequence parameters and hardware tailored specifically to the intended purpose. Second, the temporal resolution of fMRI is much finer than that of PET. Using PET, blood flow measurements of a tracer (e.g. $H_2{}^{15}O$) provide a view of activity that integrates approximately 60 s of stimulation (a snapshot with a 60 s exposure). Data can be acquired with fMRI more rapidly than the blood flow can change (between 3 and 7 s). This is used to advantage in many of the studies cited and for the event-related imaging discussed below. Third, the technique is particularly well suited to single-subject analysis because enough data can be collected from a subject to obtain statistically reliable observations. Investigations of patients and procedures can thus be addressed that would be difficult with a grouped cohort of subjects.

Event-related imaging

Event-related fMRI is a new class of experimental design within functional neuroimaging that exploits the superior temporal resolution of fMRI. Unlike the previous fMRI and PET approaches, which blocked together relatively long (e.g. 30–60 s) periods of similar behavioral trials or conditions and examined average neural response over that time period, event-related fMRI documents the neural response during each individual trial or short behavioral period. So, for example, instead of determining a cumulative response signal covering a minute of repeated thermal applications (a typical PET design), event-related fMRI could be used to examine the magnitude and time course of neural response for each of the individual, brief thermal applications. This approach has much in common with traditional evoked-potential electrophysiology, and offers many advantages in experimental design. Because different trial types can be randomly intermixed (for example, pulses of 35°, 47° and 50° administered at random every 4 s or so) and then separated for analysis, order effects and habituation can be not only controlled for, but investigated. One could compare 50° trials that followed another 50° trial to 50° trials that followed a 35° trial. This technique also offers advantages for designing experiments explicitly to examine interactions between nociception and cognitive factors (e.g. by intermixing trials that are attended to or not, or anticipated or not). Interaction or competition with other sensory modalities could also be investigated. Regional differences in the latency of neuronal response could also, in principle, be examined using this technique. Event-related fMRI has very recently come into wide use in cognitive neuroimaging, and one study [40••] has used this method to examine phasic pain stimuli. As the advantages of this approach become more well known, it will undoubtedly be the wave of the future in fMRI of pain, at least when the study of phasic, rather than tonic, nociception is the goal and when complex interaction studies are performed. The technique, as applied mainly to cognitive investigations, is further described by Menon and Kim [41] and D'Esposito *et al.* [42].

Another advantage of the spatial resolution of fMRI is the potential to analyze, at very high resolution, small regions of cerebral cortex. A recent study of the hand area of the SI [43] demonstrated the somatotopic map of the hand within the postcentral gyrus. With enough spatial resolution, distinct subregions in a particular gyrus could be resolved and provide a 'functional' cytoarchitectonic map. For example, when stimulating a receptive field on the skin would light touch be spatially distinguished from pain within the postcentral gyrus? With the appropriate paradigm, could similar fine functional mapping be performed in the insular cortex?

Radioligand studies

The imaging of the neurochemistry underlying the activity changes will add an entirely new dimension to functional brain imaging. Where one could predict a point of diminishing return from the assessment of brain activation patterns, we see no end to the ability to probe neurotransmitter function, signal transduction, neuronal plasticity and neuropathology with tracers for receptors and other molecules. Unfortunately, obtaining a suitable tracer for a receptor subtype involves considerable

medicinal chemistry and preclinical and radiochemical development in comparison to the implementation of current blood flow procedures.

Fortunately, there has been some progress in this area over the review period. Not surprisingly, for the pain field the papers all deal with opioids. One study [44] demonstrated both sex and age-related changes in the μ opioid receptor subtype using the selective tracer [^{11}C]carfentanil. The receptor content tended to increase with age and women had higher μ binding in several cortical and subcortical regions in comparison to men. This same group has produced a ^{123}I labelled diprenorphine analog for SPECT imaging; this compound is a weak partial agonist at all three receptor (μ, δ and κ) subtypes [45]. ^{11}C-labelled diprenorphine has been used to map binding sites in the human cerebellum [46] and changes in opioid binding in a patient with central pain [47•]. This patient also underwent a [^{18}F] fluorodeoxyglucose scan and data were compared with 11 normal individuals. The subject showed decreased binding in the right cortex, orbitofrontal cortex and anterior cingulate. At the same time these regions were apparently 'functionally intact' because the [^{18}F] fluorodeoxyglucose labelling was not altered in comparison with the normal database. The authors attribute the decrease in binding to enhanced competition with endogenous ligand, reflecting increased activity in neurons that synthesize and release endogenous opioid peptides. The loss of receptor sites is another possible explanation and, although this was an excellent case report, it is hard to make a generalized conclusion from these data.

Conclusion

The imaging of pain is reaching a new stage of maturity as the basic neural systems that participate are identified and fMRI techniques are utilized more extensively. Progress in understanding pathological pain states is still slow but is proceeding. However, brain imaging techniques need to be used more intensively to investigate questions related to anesthesiology and the mechanisms of pain control. For example, what happens to brain activity with complete spinal anesthesia? Is there selectivity to nociceptive suppression with spinal opioids? What about inhalation anesthetics? Can event-related fMRI be used to understand opioid actions more fully? What about postoperative pain and interventions for pain relief? There are many unanswered questions that can be addressed with the use of imaging techniques. In an earlier study [48••], we observed that strong pain from capsaicin injection produces a transient decrease in global cerebral blood flow, which is probably caused by sympathetic activation. It is possible that intra-operative manipulations also trigger this response, but the ability of anesthetic procedures to blunt the global cerebral blood flow decrease is not known. Interventions that manipulate the pain brain map should thus be an active area for further investigation.

References and recommended reading

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- • of special interest
- •• of outstanding interest

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